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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/167,088	10/06/98	FINKELMAN	F 91830/625

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EXAMINER	
GABEL, G	
ART UNIT	**PAPER NUMBER**
1641	10

DATE MAILED: 09/13/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/167,088	Finkelman et al.
Examiner	**Group Art Unit**
Gail ne R. Gabel	1641

☒ Responsive to communication(s) filed on *Aug 18, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-23 and 25-42* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-23 and 25-42* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/18/00 has been entered.

Claims 1, 12, and 34 have been amended. Claim 24 has been canceled. Accordingly, claims 1-23 and 25-42 are pending and under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-23 and 25-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, step (h) stand confusing because it appears to claim a correlation step between the amount of target analyte that is determined and the amount of targeting moiety:target analyte

conjugate bound to the capture moiety that is detected but fails to specifically indicate the relationship therebetween. For example, is the amount of targeting moiety:target analyte conjugate bound to the capture moiety that is detected indicative of the concentration of target analyte present in the blood sample.

Claim 6 is indefinite in reciting acronyms. Acronyms or abbreviations must be fully defined at least one time in a given set of claims.

Claim 7 is vague, indefinite, and indeterminate in scope in reciting "extracellular fluid" because it is unclear what is encompassed by the term as recited in the claim.

Regarding claim 8, the phrase "fragments thereof" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "fragments thereof"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d).

Claims 20, 22, and 23 are confusing in reciting a "second targeting moiety" which appears to encompass the "capture moiety" in claim 1. If so, consistent language should be used to reference a same element or otherwise, if different, be referenced so as to make necessary connections defining the cooperative relationship between the terms used.

Claim 26 lacks antecedent support in reciting "the molecule capable of binding".

Claim 37 is indeterminate in scope, recites inconsistent language and lacks antecedent support in reciting "paratopic molecules", first and second occurrences since claim 1 to which it is dependent upon recites "targeting moiety" and "capture moiety". See also claims 38 and 39.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

3. In light of applicants' argument, the rejections of claims 1-42 under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed, had possession of the claimed invention, is hereby, withdrawn.

4. Claims 1-23 and 25-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for in vivo targeting, capturing, and measuring secreted analytes such as cytokine in the blood from the circulatory system, does not reasonably provide enablement for in vivo targeting, capturing, and measuring other analytes such as proteins secreted in other body fluids such as in cases of infection in synovial fluid, cerebrospinal fluid, urine and other extracellular fluid systems. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As set forth in In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of the experimentation necessary, the

amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of prior art, the relative skill of those in the art, and the breadth of the claims.

As to the target analyte, the direction and guidance in the specification is notably limited to specifically targeting cytokines in vivo in the blood by injecting excess concentrations of specific monoclonal antibodies and allowing them to circulate the vascular system so as to allow capture of cytokines. The working examples are, likewise, limited to in vivo targeting of cytokines in the peripheral blood by antibodies prior to obtaining a blood sample so as to effect complexation therebetween to subsequently obtain accurate measure of concentration of cytokines therein. While this is sufficient guidance and direction for in vivo targeting, capturing, and measuring of concentration of endogenous cytokines from blood samples, one of the skill in the art would not know how to target in vivo and capture other macromolecular and protein target analytes such as fibrinogen, albumin, and glycoproteins in the blood or in other body fluids including enzymes from saliva, interstitial fluid, CSF, synovial fluid, and urine, without undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. In light of applicants' submission of declaration, amendment, and arguments, the rejection of claims 1-42 under 35 U.S.C. 103(a) as being unpatentable over Tamarkin et al. (US 5,587,294) in view of Finkelman et al. (Journal of Immunology, 1993) and in further view of Pouletty et al. (US 5,612,034) is hereby, withdrawn.

6. In light of applicants' submission of declaration, amendment, and arguments, the rejection of claims 1-42 under 35 U.S.C. 103(a) as being unpatentable over Tamarkin et al. (US 5,587,294) in view of David et al. (US 4,486,530) and Gosling (Clin. Chem., 1990), in further view of Finkelman et al. (Journal of Immunology,1993), and in further view of Pouletty et al. (US 5,612,034) is hereby, withdrawn.

New Ground of Rejection

7. Claims 1-23 and 25-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamarkin et al. (US 5,587,294) and Pouletty et al. (US 5,612,034) in view of David et al. (US 4,486,530).

Tamarkin et al. and Pouletty et al. have been discussed in Paper No. 3.

David et al. has been discussed in Paper No. 5.

To reiterate, Tamarkin discloses a competitive solid phase immunoassay for measuring the concentration of proteins, especially endogenous cytokines in the blood and other body fluids such as saliva, nasal secretions, tears and sweat in humans and animals (see Summary). The immunoassay may be enzyme immunoassay or it may utilize other labels such as fluorescent labels, radioactive elements, or luminescent labels (see column 7, lines 13-20, column 11, line 13 to column 12, line 11). Thereafter, detection of the labeled antibody or binding partner for the labeled analyte is accomplished by a chromogenic substrate, fluorometer, or a scintillation counter (see column 12 20-29). Tamarkin discloses that in polyclonal-antibody based "one-site" immunoassay wherein a cytokine may be bound to another molecule (such as cytokine binding proteins) in the biological fluid, there is at least one part of the molecule that is available for site recognition (see column 9, lines 10-16). Initially, the body fluid sample is incubated in the presence of an antibody capable of binding to the cytokine and then the amount of cytokine-bound or unbound antibodies are measured (see column 9, lines 48-53). A polyclonal antibody which recognizes many epitopes on the cytokine molecule is adsorbed to a solid phase support or carrier. This polyclonal antibody is the capture antibody which is used to bind the labeled

analyte, i.e. biotinylated IL-1, in order to form an antibody-analyte complex (column 10, lines 18-43). The amount of cytokine in the complex is detected by the addition of streptavidin conjugated to an enzyme, i.e. alkaline phosphatase, followed by the addition of a chromogenic substrate -nitrophenyl phosphate (see column 10, lines 47-63 and column 11, lines 13-28). Tamarkin further discloses a kit for measuring cytokine incorporating, therewith, biotin as a label, polyclonal capture antibody as the first binding partner, enzyme conjugated streptavidin as the second binding partner (see column 14, lines 38-46). Tamarkin also discloses the use of a kit incorporating therein all necessary reagent for use in measuring cytokine production in body fluids.

Tamarkin fails to teach injecting a targeting moiety to a human or animal in order to form a targeting moiety: target analyte complex. Further, Tamarkin fails to use immunometric sandwich assay using monoclonal antibodies in measuring the concentration of proteins such as antigens in a sample.

Pouletty discloses injecting a targeting moiety (binding entity) into the bloodstream of mammalian hosts for binding with target analytes: proteins such as albumin and transferrin (see column 2, lines 25-44). The targeting moiety is a small molecule that is haptenic such as biotin or a ligand for a naturally occurring receptor or a substrate for an enzyme (see column 3, line 60 to column 4, line 9). Pouletty further discloses a second targeting moiety (second binding entity) which provides relatively high specificity and affinity such as membrane proteins, enzymes, or avidin (see column 6, lines 37-53). The targeting moiety is administered via injection

intravenously (see column 4, lines 40-50). The target analytes include cytokines, interleukins, growth factors, and interferons (see column 7, line 47 to column 8, line 16). A bolus of the targeting moiety will bind to enable reaction of active compounds with active functionalities of proteins, thereby, creating a population of vascular functionalized proteins. In essence, Pouletty discloses that the targeting moiety specifically binds the target analyte in vivo so as to allow for "capture" of the target analyte.

David discloses a two-site or sandwich immunometric assay for determining the concentration of target analyte (antigenic substances) in fluids using monoclonal antibodies (see Abstract). David specifically discloses unlabeled antibody bound to a solid support and at least one or usually two or more labeled monoclonal soluble antibodies carrying a fluorescing or quenching chromophore, each antibody specific to a single antigenic site (see column 4, lines 51-68). Reverse and simultaneous immunometric assays can be conducted wherein a complex of labeled antibody:antigen will preclude formation of a complex between the antigen and antibody bound to the solid phase (see column 6, lines 54-68).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have injected a targeting moiety into peripheral blood circulation of a human patient for binding with target analyte as taught by Pouletty then to have obtained a blood sample containing the analyte conjugated with the targeting moiety in order to acquire an accurate measure of endogenous proteins such as cytokines from the blood of the patient using competitive solid phase immunoassay such as taught by Tamarkin because Tamarkin specifically disclosed the

difficulty in obtaining accurate measure of soluble proteins because of the masking effect by *binding proteins* in the blood and by specifically targeting the analyte using a specific targeting moiety for the purpose of capturing by conjugation thereto, the masking effect of *binding proteins* in the subsequent quantification of the analyte can be decreased, thereby providing an accurate measure of said analyte. One of ordinary skill in the art would have reasonable expectation of success in substituting sandwich immunoassay technique using labeled soluble monoclonal antibodies as taught by David into the competitive solid phase enzyme immunoassay as taught by Tamarkin because David specifically taught that sandwich immunometric assays are conventional and well-known in the art to be well-suited for the detection of polyvalent antigens using the combined selectivity of two antibodies which therein lies the motivation for one of ordinary skill in the art to substitute such method, that is for its heightened sensitivity and accuracy through "inherent" initial complexation of excess amounts of labeled monoclonal antibodies with and specific for the target analyte.

Response to Argument

8. Applicants' arguments filed 8/18/ 2000 have been fully considered but are now moot in light of the new ground of rejection. Accordingly, no claims are allowed.

Remarks

9. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

Senger et al. (US 6,022,51) disclose immunological preparations for concurrent specific binding to a vascular permeability factor bound in vivo to a tumor associated blood vessel.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Friday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays at 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

9/9/00

Gailene R. Gabel
Patent Examiner
Art Unit 1641

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